General

Guideline Title

Therapeutic monitoring of TNF-alpha inhibitors in Crohn's disease (LISA-TRACKER ELISA kits, IDKmonitor ELISA kits, and Promonitor ELISA kits).

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Therapeutic monitoring of TNF-alpha inhibitors in Crohn's disease (LISA-TRACKER ELISA kits, IDKmonitor ELISA kits, and Promonitor ELISA kits). London (UK): National Institute for Health and Care Excellence (NICE); 2016 Feb 17. 52 p. (Diagnostics guidance; no. 22).

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

The LISA-TRACKER, IDKmonitor and Promonitor enzyme-linked immunosorbent assay (ELISA) kits show promise for therapeutic monitoring of tumour necrosis factor α (TNFα) inhibitors in people with Crohn's disease but there is insufficient evidence to recommend their routine adoption across the National Health Service (NHS).

Laboratories currently using LISA-TRACKER, IDKmonitor and Promonitor ELISA kits for therapeutic monitoring of TNFα inhibitors in people with Crohn's disease whose disease loses response to TNFα inhibitors should:

- Have specialist expertise in immunoassay analysis, including an understanding of the technical factors that may affect the results of the ELISA kits
- Work closely with the treating or referring clinician, in a network, to ensure appropriate use of the tests and interpretation of the results
- Work with clinicians to collect data through a prospective study, for local audit, or for submission to an existing registry. (The Inflammatory Bowel Disease [IBD] Registry is being adapted to receive data on TNFα inhibitor levels and antibodies against TNFα inhibitors. When this facility is available, all data should be entered onto the database [see Section 7.2 of the original guideline document].).

Further research is recommended on the clinical and cost-effectiveness of using LISA-TRACKER, IDKmonitor and Promonitor ELISA kits for therapeutic monitoring of TNFα inhibitors in people with Crohn's disease whose disease responds to treatment with TNFα inhibitors (see section 7.3 of the original guideline document).

Note: This guidance considers ELISA kits for therapeutic monitoring of TNFα inhibitors in 2 different populations:

- People with Crohn's disease, whose disease loses response to treatment with TNFα inhibitors (that is, people whose disease first responds to treatment, but stops responding over time, so may need a higher dose of TNFα inhibitor to try to recover a clinical response)
- People with Crohn's disease, whose disease responds to treatment with TNFα inhibitors (that is, people whose disease responds well to treatment and who may continue having the same level of treatment)

People whose disease does not respond to treatment in the induction phase of treatment are not considered in this assessment.

Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy was published while this guidance was in development. The National Institute for Health and Care Excellence (NICE) will consider adding vedolizumab into the economic model as a treatment option in the care pathway of people with Crohn's disease when the diagnostics guidance is reviewed for the need to update.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Crohn's disease

Guideline Category

Evaluation

Technology Assessment

Clinical Specialty

Family Practice

Gastroenterology

Internal Medicine

Pathology

Intended Users

Advanced Practice Nurses

Clinical Laboratory Personnel

Physician Assistants

Physicians

Guideline Objective(s)

To evaluate the clinical effectiveness and cost-effectiveness of using enzyme-linked immunosorbent assay (ELISA) kits (LISA-TRACKER, IDKmonitor and Promonitor) to test levels of tumour necrosis factor α (TNFα) inhibitors and antibodies to TNFα inhibitors in people with Crohn's

disease

Target Population

- People with Crohn's disease whose disease loses response to treatment with tumour necrosis factor α (TNFα) inhibitors (that is, people whose disease first responds to treatment, but stops responding over time, so may need a higher dose of TNFα inhibitor to try to recover a clinical response)
- People with Crohn's disease whose disease responds to treatment with TNFα inhibitors (that is, people whose disease responds well to treatment and who may continue having the same level of treatment)

Note: People whose disease does not respond to treatment in the induction phase of treatment are not considered in this assessment.

Interventions and Practices Considered

LISA-TRACKER, IDKmonitor and Promonitor enzyme-linked immunosorbent assay (ELISA) kits for therapeutic monitoring of tumour necrosis factor α (TNFα) inhibitors

Major Outcomes Considered

- Clinical effectiveness
  - Sensitivity and specificity of the assays
  - Response rate based on Crohn's Disease Activity Index (CDAI) score
  - Any measure of change in severity of Crohn's disease including physicians global assessment
  - Duration of response
  - Relapse and remission
  - Rates of hospitalisation
  - Rates of surgical intervention
  - Time to surgical intervention
  - Adverse effects of treatment
  - Health-related quality of life
  - Time to result
  - Number of inconclusive results
  - Frequency of dose adjustment
  - Frequency of treatment switch
- Cost-effectiveness

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this diagnostic guidance and prepare a

Diagnostics Assessment Report (DAR). The DAR for this diagnostic guidance was prepared by Warwick Evidence (see the "Availability of Companion Documents" field).

Clinical Effectiveness Review

Search Strategies for Clinical Effectiveness

An iterative procedure was used to develop the initial Medline search, with reference to Assessment Group's own scoping searches and those undertaken by information specialists at NICE. Known articles were consulted and checked for relevant terms. Additional phrases were added to find relevant articles that did not include terms for the test name or type of test or population in title, abstract or indexing. This search developed for Medline was adapted as appropriate for other databases and sources. The searches for each source are provided in Appendix 3 of the DAR. Searches for studies for cost and quality of life were developed separately.

The search strategy comprised the following main elements:

- Searching of electronic bibliographic databases
- Contact with experts in the field
- Scrutiny of references of included studies
- Screening of manufacturers' and other relevant organisations' Web sites for relevant publications

Bibliographic Databases

MEDLINE; MEDLINE In-Process & Other Non-Indexed Citations; EMBASE; Cochrane Library (including Cochrane Systematic Reviews, Database of Abstracts of Reviews of Effects [DARE], CENTRAL, National Health Service Economic Evaluation Database [NHS EED], and Health Technology Assessment [HTA] databases); Science Citation Index and Conference Proceedings (Web of Science); Index to Theses; DART-Europe; Dissertations & Theses; National Institute for Health Research (NIHR) Health Technology Assessment Programme; PROSPERO (International Prospective Register of Systematic Reviews).

The following trial and patent databases were also searched: Current Controlled Trials; ClinicalTrials.gov; United Kingdom Clinical Research Network (UKCRN) Portfolio Database; World Health Organization (WHO) International Clinical Trials Registry Platform; Espacenet (European Patent Office).

Specific conference proceedings, selected with input from clinical experts and Specialist Committee Members, were also checked for the last five years:

- European Crohn’s and Colitis Organisation (ECCO)
- Digestive Diseases Week (DDW) (meeting of the American Gastroenterology Association [AGA])
- British Society of Gastroenterology (BSG)
- United European Gastroenterology Week (UEGW)
- American College of Gastroenterology

See the DAR for the list of various health services research agencies, regulatory bodies, professional societies, and manufacturers that were consulted via the Internet.

The reference lists of included studies and relevant review articles were checked. Citation searches of selected included studies were undertaken using Scopus. Identified references were downloaded in Endnote X7 software. Included papers were checked for errata using PubMed. Database searches were undertaken in October and November 2014.

Refer to Section 3.1.2.1 for detailed inclusion and exclusion criteria for the different objectives.

Using the Information Provided by the Manufacturers

The information provided by the manufacturers (see Appendix 4 of the DAR for an itemised list of documents received) was screened for three purposes:

1. Additional studies not identified by DAR searches
2. Information for the technical description of the three intervention assays
3. Information on assay comparisons

Additionally, the Assessment Group sought detailed information from the manufacturers by e-mail regarding mechanisms and reactants (in

particular specificities and properties of antibodies and other reagents) employed in the three intervention enzyme-linked immunosorbent assay (ELISA) tests.

Review Strategy

The general principles recommended in the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement were used. Records rejected at full text stage and reasons for exclusion were documented. Two reviewers independently screened the titles and abstracts of all records identified by the searches and discrepancies were resolved through discussion. Disagreement was resolved by retrieval of the full publication and consensus agreement. Full copies of all studies deemed potentially relevant were obtained and two reviewers independently assessed these for inclusion; any disagreements were resolved by consensus or discussion with a third reviewer.

Search Results

Figure 6 in the DAR provides the PRISMA flow diagram for Objectives A, B and C. A total of 2,428 records were identified through electronic searches. Six additional records were identified from other sources. The removal of duplicates left 1,616 records to be screened, of which 1,359 were excluded at title/abstract level as these were irrelevant to the decision questions. The remaining 257 records were examined for inclusion at full-text, of which 70 (reported in 68 studies) were included in the clinical effectiveness review. Table 5 of the DAR summarises the 68 included studies and refers the reader to the relevant section where they are covered. Details on the reasons for excluding studies at full text can be found in Appendix 6 of the DAR.

The search of on-going trials in ClinicalTrials.gov, Current Controlled Trials, UKCRN Portfolio, and World Health Organization International Clinical Trials Registry Platform (WHOICTRP) databases (carried out between 4th and 11th November 2014) retrieved 7 relevant ongoing trials (see Appendix 7 of the DAR).

Cost-effectiveness Review and Health Economic Modelling

Systematic Review of Existing Cost-effectiveness Evidence

Search Strategy

A comprehensive search of the literature for published economic evaluations (including any existing models), cost studies and quality of life (utility) studies was performed. The systematic search included searching the following electronic databases during December 2014 (from the 12th to 17th December):

- MEDLINE (Ovid) - 1946 to Week 3 November 2014
- MEDLINE In-Process Citations and Daily Update (Ovid) - December 11, 2014
- EMBASE (Ovid) - 1947 to 15 December 2014
- NHS Economic Evaluation Database (NHS EED) (Cochrane Library)
- Science Citation Index (Web of Knowledge) - 1970–present
- Cost-effectiveness analysis (CEA) registry
- EconPapers (RePEc)
- School of Health and Related Research Health Utilities Database (ScHARRHUD)

The search included terms for Crohn's disease, anti-tumour necrosis factor α (TNFα) drugs and the different assay kits, combined with economic and quality of life terms. The search was limited to studies published in the English language. The search strategy developed was based on the clinical effectiveness review with input from a health economist. Details of the full search strategies are provided in Appendix 3 of the Assessment Report.

Inclusion Criteria

Only studies meeting the following inclusion criteria were included in the review:

- Study type: Fully published economic evaluations (including economic models)
- Population: People with Crohn's disease
- Intervention: Anti-TNFα drugs (adalimumab and infliximab) and antibody drug testing (LISA-TRACKER ELISA kits, TNFα-Blocker ELISA kits, and Promonitor ELISA kits) for any dosage or treatment regimen
- Comparator: Standard care treatment - anti-TNFα drugs (adalimumab and infliximab) for any dosage or treatment regimen
- Outcomes: Cost-effectiveness or cost-utility studies reporting outcomes as clinical effectiveness measures or utility measures (utility, EuroQuol 5-dimension scale [EQ-5D] or short form 6D [SF-6D] score or quality-adjusted life years ([QALYs]).

Exclusion Criteria

Studies meeting the following exclusion criteria were excluded from the review:

- Non-English-language publications
- Studies in the health areas where these anti-TNFα drugs have also been used for diseases such as ulcerative colitis, rheumatoid arthritis, psoriasis, and tuberculosis

Search Results for Objective D

The literature search identified 2,466 records through electronic database searches and other sources. After removing duplicates, 1,527 records were screened for inclusion. On the basis of title and abstract sift only, 1,518 records were excluded. The remaining nine records were included for full-text screening. A further five articles were excluded at the full-text stage, as these studies did not contain any assay kits for measuring levels of TNFα inhibitors and anti-drug antibodies. The literature search identified four studies which included cost-effectiveness of different assay kits for measuring levels of TNFα inhibitors and of anti-drug antibodies (see Figure 27 of DAR for the PRISMA diagram of cost-effectiveness studies).

Number of Source Documents

Clinical Effectiveness

- Sixty-eight studies represented by 70 articles were included.
- Seven relevant ongoing trials were also included.

Figure 6 in the Diagnostics Assessment Report (DAR) (see the "Availability of Companion Documents" field) provides the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) flow diagram for Objectives A, B and C.

Cost-effectiveness

- Four studies describing cost-effectiveness of different assay kits for measuring levels of tumour necrosis factor α (TNFα) inhibitors and of anti-drug antibodies were included.
- An economic model was presented.

See Figure 27 in the DAR for a PRISMA flow diagram for Objective D.

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Note from the National Guideline Clearinghouse (NGC): The National Institute for Health and Care Excellence (NICE) commissioned an independent academic centre to perform a systematic literature review on the technology considered in this diagnostic guidance and prepare a Diagnostics Assessment Report (DAR). The DAR for this diagnostic guidance was prepared by Warwick Evidence (see the "Availability of

Companion Documents" field).

Clinical Effectiveness Review

Data Extraction Strategy

Data were extracted by one reviewer, using a piloted data extraction form. Completed data extraction forms are available in Appendix 5 of the DAR. A second reviewer checked the extracted data and any disagreements were resolved by consensus or discussion with a third reviewer.

See Section 3.1.5 of the DAR for the quality assessment strategy.

Methods of Analysis/Synthesis

Objective A - Review of Comparative Performance of Tests

The Assessment Group mapped included studies according to the comparisons they undertook. A narrative was produced to summarise the studies which compared the performance of the intervention assays and assays suitable for a linked evidence approach and considering the concordance between the tests. This was assessed using the following outcomes:

1. Concordance between tests (split by reference standard results positive and reference standard results negative or clinical outcomes where available) for therapeutic drug and detectable anti-drug for all index tests and comparators
2. Characteristics of cases where there was disagreement and agreement between tests
3. Bland-Altman plots to show patterns of correlation

The specific measures of concordance used were percentage agreement between the tests (split between reference standard results positive and reference standard results negative samples where available) and Cohen's Kappa. Two main secondary outcomes were also collected. Firstly, characteristics of cases where there was disagreement and agreement between tests, which may provide information about the reason for and implications of the discordant results. Secondly, the shape of the Bland-Altman plots as the plot shows whether the difference between the two tests is dependent on absolute drug and anti-drug levels. Mean bias and the upper and lower limits of agreement were not particularly informative here as the Assessment Group is only interested in one cut-point not the whole range of concentrations. Pearson's correlation coefficient was not considered in detail as it can have high values even when clinically meaningful differences are present. Where there were sufficient studies, meta-analysis of Cohen's Kappa was considered.

Objective B - Description of Algorithms Prescribing Patient Management Following Test Outcomes for Drug and/or Anti-drug Antibody Levels

Algorithms used in management studies were described narratively and compared to the algorithm adapted from Scott and Lichtenstein (2014) (for loss of response) and to the algorithm adapted from Vande Casteele et al. (2015) (for responders). Patients or decisions non-compliant with the stated algorithm were quantified. Time of testing, sequence of testing (drug and antibodies) and sequence of analysis were also considered.

Objective C1 - Clinical Studies Evaluating Drug Monitoring for the Management of Crohn's Disease Patients (Management Studies)

Depending on the available evidence, analyses were stratified according to the type of enzyme-linked immunosorbent assay (ELISA) or other assay, type of drug (infliximab or adalimumab) and patient group (patients with loss of response or responders).

Study, treatment, population, and outcome characteristics were summarised and compared qualitatively and where possible quantitatively in text and graphically and in evidence tables. Pooling study results by meta-analysis was considered; however, meta-analysis was unsuitable for the data identified and the Assessment Group employed a narrative synthesis using text and tables. A detailed commentary on the major methodological problems and biases affecting the studies was also included, together with a description of how this may have influenced individual study results.

The Assessment Group used a linked-evidence approach. Evidence on outcomes reported by studies using other test methods (radioimmunoassay, liquid-phase mobility shift assay, in-house ELISAs) for patient management was linked to evidence on comparative test performance between the Assessment Group's intervention tests and these other methods to allow for estimates of anticipated outcome for intervention assays.

Time of testing, sequence of testing (drug and antibodies) and sequence of analysis were also considered.

Where relevant Kaplan-Meier plots were available, individual patient data (IPD) was reconstructed using the method of Guyot 2013. Parametric models were fitted to reconstructed IPD using STATA version 11.

Objective C2

For Objective C2 the Assessment Group aimed to:

a. Provide an overview of meta-analyses of studies addressing the relationship between drug and/or anti-drug antibody levels and clinical state of patients with Crohn's disease by producing a narrative of identified systematic reviews with meta-analyses, presenting the reported meta-analyses results, and undertaking hierarchical meta-analysis of the data presented in the systematic reviews.
b. Pool test accuracy data for prediction of patients' clinical state (response or lost response). This was done as a potentially useful supplement to management studies for informing the economic model.

Studies which provided dichotomised test results and related these to dichotomised clinical status were identified. In particular studies were sought that reported on both drug and anti-drug antibody test results for individual patients. Two by two data for tests were extracted, together with the type of test employed (e.g., ELISA, radio-immunoassay [RIA], homogeneous mobility shift assay [HMSA]), the anti-tumour necrosis α [TNFα] administered, dose regimen, patient inclusion and exclusion criteria, timing of testing, method for establishing clinical status, test cut-off used, and study design were noted where these were reported. The populations of interest were: a) responders and responders who lost response; b) patients with loss of response who continued with loss of response or who regained a response.

Meta-analyses of single test studies were undertaken: a) to provide a pooled estimate for the probability of returning a specified test result after trough anti-TNFα testing (useful for estimating reflex strategy test result probabilities); b) to provide pooled estimates for the probability of returning a specified test results by single test (i.e., anti-TNFα or anti-drug antibodies) that can be compared for consistency with the corresponding probabilities from the few identified patient level studies.

Review Manager (RevMan) 5.3 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) was used for analysis of sensitivities and specificities. Meta-analysis was undertaken in STATA version 11 using the metandi package. The prevalence of clinical status was meta-analysed using random effects model with "MetaAnalyst" software.

Given the prevalence (P) of the condition tested for, and the joint sensitivity (Sens) and specificity (Spec) values from meta-analysis, the probability of returning a positive test result is: Positive test = [P * Sens] + ([1-P]*[1-Spec])

And the probability of returning a negative test result is: Negative test = ([1-P] * Spec) + (P*[1-Sens])

See Section 3 of the Assessment Report for additional information on clinical effectiveness analysis.

Cost-effectiveness Review and Economic Modelling

Systematic Review of Existing Cost-effectiveness Evidence

Assessment of Eligibility and Data Extraction

All retrieved records (citations and abstracts) were collected in a specialist database (Endnote) and duplicate records were identified and removed. Two reviewers independently reviewed titles and abstracts to identify potentially relevant papers for inclusion. Any discrepancies were resolved by discussion. See Appendix 13 of the DAR for the table of full text studies excluded with reason.

Data extraction was carried out in two stages by one reviewer using standardised data extraction sheets (see Appendix 14 of the DAR) and was then checked by a second reviewer. Stage one considered all eligible studies (fully published economic evaluations including any economic models) and stage two considered studies assessed for usefulness for populating the economic model. Data extracted during stage one included the following:

- Study details: author names, source of publication, language and publication type
- Baseline characteristics: population, intervention, comparators, outcomes, and type of economic evaluation
- Methods: target population and subgroups, setting and location, study perspective, time horizon, discount rate, measurement of effectiveness, measurement and valuation preference based outcomes, resource use and costs, currency, price date and conversion, model type, assumptions and analytical methods
- Results: study parameters, incremental costs and outcomes and characterising uncertainty
- Discussion: study findings, limitations, generalisability and conclusions
- Other: sources of funding, conflicts of interest and comments

Quality Assessment

The quality of full economic evaluation studies that were identified were assessed using the consolidated health economic evaluation reporting standards (CHEERS) checklist (see Appendix 15 of the DAR) by one reviewer and cross-checked by a second reviewer. The CHEERS checklist comprises six dimensions which include title and abstract, introduction, methods, results, discussion and other. Under these dimensions, a

series of questions check whether the criteria have been clearly reported. Any studies containing an economic model were further assessed using the framework for the quality assessment of decision analytic modelling by Philips et al. (2004) (see Appendix 15 of the DAR). The Philips' checklist contains two main dimensions, structure of the model and data used to parameterize the model. Under these dimensions several questions assess whether the criteria have been clearly reported.

Data Synthesis

Information extracted from the included studies were summarised and tabulated. Findings from individual studies were compared narratively.

Considerations of Using the Former Health Technology Assessment (HTA) Model by Dretzke et al. (2011) to Inform the Current Model Structure

The previous HTA model used natural history data which is now outdated. The current model for the standard care arm is restricted to starting with infliximab (through lack of data for adalimumab) but otherwise adopts the general approach used in the HTA model, however using updated natural history data (for surgery, for maintenance of response, for dose escalation, and for other minor parameters, together with more recent clinical expert advice). Clearly the HTA model structure is not easily transferable to the current intervention arm since the latter requires considerable added complexity since it is based on drug and anti-drug antibody testing; however, this arm conforms to the HTA approach and is designed for comparison with standard care on infliximab.

Health Economic Methods

Developing the Model Structure

The Assessment Group developed a Markov model using TreeAge Pro 2013 software program (TreeAge Software, Williamstown, MA, USA). The model was developed with clinical input, and represents the clinical pathway people would undergo while being treated for moderate to severe Crohn's disease. The illustrative model structures for responders and for those who lose response is shown in Figures 29 and 30 of the DAR, respectively. More detailed decision trees on the patient pathways can be found in Appendix 16 of the DAR. In the models, concurrent and reflex testing conducted every three months were compared to standard care for responders and those who experience loss of response:

- Standard care
- Concurrent testing: testing for TNFα inhibitor levels and antibodies to TNFα inhibitors
- Reflex testing: testing for TNFα inhibitor levels followed by testing of antibodies to TNFα inhibitors depending on the drug test level

NICE guidance on model-based economic analyses suggests adopting a time horizon long enough to capture the costs and effects of an intervention; normally a lifetime horizon, because chronic conditions may reduce life expectancy. To the Assessment Group's knowledge, no clinical trials exist that provide evidence of significant difference between testing and standard regimens in Crohn's disease mortality. Hence, they assumed a 10-year time horizon with four-week cycle lengths to be appropriate to capture all benefits of testing and treatment.

Table 27 of the DAR shows the health states required for the responder and loss of response models.

See Section 4 of the DAR for additional information on cost-effectiveness analysis.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Developing Recommendations

After reviewing the evidence the Diagnostic Advisory Committee (DAC) agrees draft recommendations on the use of the technology in the National Health Service (NHS) in England. When formulating these recommendations, the Committee has discretion to consider those factors it believes are most appropriate to the evaluation. In doing so, the Committee has regard to any relevant provisions of the National Institute for Health and Care Excellence's (NICE's) Directions, set out by the Secretary of State for Health, and legislation on human rights, discrimination and equality. In undertaking evaluations of healthcare technologies, NICE takes into account the broad balance of clinical benefits and costs, the degree of clinical need of patients under consideration, any guidance issued to the NHS by the Secretary of State that is specifically drawn to the attention of NICE by the Secretary of State, and any guidance issued by the Secretary of State, and the potential for long-term benefits to the

NHS of innovation.

The Committee takes into account advice from NICE on the approach it should take to making scientific and social value judgements. Advice on social value judgements is informed in part by the work of NICE's Citizens Council.

The Committee takes into account how its judgements have a bearing on distributive justice or legal requirements in relation to human rights, discrimination and equality. Such characteristics include, but are not confined to: race, gender, disability, religion or belief, sexual orientation, gender reassignment and pregnancy or maternity.

The Committee considers the application of other Board-approved NICE methods policies, such as the supplementary guidance on discounting and the end-of-life criteria, if they are relevant to the evaluation.

Because the Programme often evaluates new technologies that have a thin evidence base, in formulating its recommendations the Committee balances the quality and quantity of evidence with the expected value of the technology to the NHS and the public.

The credibility of the guidance produced by NICE depends on the transparency of the DAC's decision-making process. It is crucial that the DAC's decisions are explained clearly, and that the contributions of registered stakeholders and the views of members of the public are considered. The reasoning behind the Committee's recommendations is explained, with reference to the factors that have been taken into account.

The language and style used in the documents produced by the Committee are governed by the following principles:

- Clarity is essential in explaining how the DAC has come to its conclusions.
- The text of the documents does not need to reiterate all the factual information that can be found in the information published alongside the guidance. This needs careful judgement so that enough information and justification is given in the recommendations to enable the reader to understand what evidence the DAC considered and, if appropriate, who provided that evidence.

The Committee may take into account factors that may provide benefits to the NHS or the population, such as patient convenience. It may also consider costs and other positive or negative impacts on the NHS that may not be captured in the reference-case cost analysis, such as improved processes.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

The Committee considered the assumptions used in the economic models. It noted that 2 different sets of transition probabilities were used to generate 2 sets of base-case results. The first base case used time-dependent transition probabilities, whereas the second base case used exponential transition probabilities. The Committee heard from the that the time-dependent transition probabilities best reflect the data from the key studies used to provide inputs for the model. However, the exponential transition probabilities assume that people progress through the model at a constant rate over time, and this better reflects how people move through the care pathway, given the modelling methods that were used. The Committee concluded that the results of the second base case were the most plausible.

The Committee considered the test schedules assessed in the models. It noted that in the base case, people whose disease responded to tumour necrosis factor α (TNFα) inhibitor treatment were tested for TNFα inhibitor levels and antibodies to TNFα inhibitors every 3 months. The Committee heard from a clinical expert that in UK practice the most likely testing strategy is to test for TNFα inhibitor levels and antibodies to TNFα inhibitors once a year and on loss of response. The Committee concluded that the most plausible incremental cost-effectiveness ratio (ICER) for the responder model was from the 'annual testing' scenario (£126,600 saved per quality-adjusted life-year [QALY] lost for concurrent testing compared with no testing), and the most plausible ICER for the loss of response model was from the 'testing only on loss of response' scenario (£340,900 saved per QALY lost for concurrent testing compared with no testing).

The Committee considered the QALY losses resulting from the economic model that were spread over 10 years. It noted that in the responder model with annual testing, the QALY losses compared with a no-testing strategy were 0.280 for a reflex-test strategy and 0.288 for a concurrent-test strategy. It also noted that in the loss of response model, when testing was done only in people whose disease lost response to a TNFα inhibitor, the QALY losses compared with a no-testing strategy were 0.333 for a reflex-test strategy and 0.351 for a concurrent-test strategy. The Committee considered that these QALY losses are quite large and unexpected, given the low quality of life experienced by people with Crohn's disease that loses response to a TNFα inhibitor. The Committee also heard from a clinical expert on the Committee that the quality of life of people

with Crohn's disease can be difficult to value, and that utility values used in the model may not fully reflect the quality of life of people with Crohn's disease. The Committee concluded further that research into the quality of life of people with Crohn's disease treated with TNFα inhibitors would be useful.

The Committee considered the reasons for the QALY losses. It heard from the External Assessment Group that one reason was the high proportion (79%) of people in the model in the loss of response health state with TNFα inhibitor present and antibodies to TNFα inhibitors absent. This proportion was taken from the study by Steenholdt et al. (2014). A clinical expert on the Committee advised that the proportion of patients in the UK with loss of response, TNFα inhibitor present and no antibodies to TNFα inhibitors is much lower than 79%. The Committee also heard from the External Assessment Group that these people in the model, with a testing strategy, would stop TNFα-inhibitor treatment and have best supportive care, which would eventually include surgery. A no-testing strategy would result in these patients staying on TNFα inhibitor treatment longer before stopping the TNFα inhibitor and having best supportive care. The Committee also noted its conclusion that the uncertainty in the accuracy of the enzyme-linked immunosorbent assay (ELISA) kits for predicting clinical state could lead to misclassifying clinical state in some people with Crohn's disease. It noted further that if clinical state in people with Crohn's disease is being misclassified by the test results this may explain some of the QALY losses seen in the economic model. The Committee concluded that the QALY losses in the models were uncertain and may not reflect clinical practice in the National Health Service (NHS).

The Committee considered the cost savings resulting from the economic model. It noted that the cost savings in the testing strategies compared with the no-testing strategy were driven by reduced use of TNFα inhibitor in the testing strategies, particularly by:

- Not increasing the dose of TNFα inhibitor in people whose disease loses response and who have high levels of antibodies to TNFα inhibitor
- Stopping treatment with, or reducing the dose of TNFα inhibitor in people whose disease is in remission and have undetectable or low trough level of TNFα inhibitor

The Committee heard from an expert on the Committee that biosimilars for infliximab and adalimumab are likely to be introduced soon. The Committee noted that biosimilar drugs are cheaper than the original drugs, which would be likely to reduce the cost savings in the model. The Committee concluded that the small evidence base led to uncertainties in the modelling, which resulted in uncertainty in the cost savings.

The Committee considered the different scenarios for using the ELISA kits, that is, in people whose disease loses response to TNFα inhibitor treatment, and in people whose disease is responding to TNFα-inhibitor treatment. The Committee noted the differences in the ICERs between the 2 scenarios, and that using the ELISA kits in people whose disease loses response to TNFα-inhibitor treatment was associated with greater savings per QALY lost compared with using the ELISA kits in people whose disease is responding to TNFα-inhibitor treatment. It also noted that there was less uncertainty in the cost savings in people whose disease loses response to TNFα inhibitor treatment compared with people whose disease was responding to TNFα-inhibitor treatment. The Committee further noted that people with Crohn's disease with loss of response to TNFα inhibitors have a low quality of life and limited treatment options (see Section 6.2 in the original guideline document). The Committee concluded that in people whose disease loses response to TNFα-inhibitor treatment, the ELISA kits should be used in laboratories alongside data collection through a relevant registry or audit. The Committee also concluded that only laboratories that are currently using these tests and have expertise in immunoassay analysis and a thorough understanding of the technical factors that may affect the results should continue to use them. These laboratories should work closely in a network with the treating or referring clinician to ensure the appropriate use of the tests and interpretation of the results. The Committee also concluded that in people whose disease responds to TNFα-inhibitor treatment, the ELISA kits should be used only in research.

See Sections 5 and 6 of the original guideline for additional discussion of the economic analysis.

Method of Guideline Validation

External Peer Review

Description of Method of Guideline Validation

The National Institute for Health and Care Excellence (NICE) sends the Diagnostics Assessment Report (DAR), with any confidential material removed, to registered stakeholders for comment. Stakeholders have 10 working days to return comments. Models supporting the DAR are made available to registered stakeholders on request during this period.

NICE presents anonymised registered stakeholder comments on the DAR, along with any responses from NICE or the External Assessment Group, to the Committee and later publishes these comments on its Web site.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

The Diagnostic Advisory Committee considered a systematic review and cost-effectiveness analysis prepared by an External Assessment Group.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Measuring levels of tumour necrosis factor α (TNFα) inhibitors and antibodies against TNFα inhibitors in a person's blood could help clinicians to identify the best treatment strategy for a person with Crohn's disease.

Potential Harms

One study was identified that has data on the LISA-TRACKER enzyme-linked immunosorbent assays (ELISAs) and the Leuven in-house ELISAs for infliximab and antibodies to infliximab. This study also included the Amsterdam Sanquin ELISA and radioimmunoassay. A mix of clinical and spiked samples was used. Results suggest that the LISA-TRACKER ELISA may give some false positive results for infliximab levels in the presence of antibodies to infliximab or adalimumab. However, these results were disputed in a non-peer-reviewed letter to the editor, which was not included in the systematic review because it did not meet the inclusion criteria. For detecting antibodies to infliximab, the LISA-TRACKER ELISA gave fewer positive results than the radioimmunoassay, but a greater number of positive results than the Leuven in-house ELISA. However, it is not clear if these results are true positives.

Qualifying Statements

Qualifying Statements

- This guidance represents the view of the National Institute for Health and Care Excellence (NICE), which was arrived at after careful consideration of the evidence available. Healthcare professionals are expected to take it fully into account when exercising their clinical judgement. However, the guidance does not override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.
- Implementation of this guidance is the responsibility of local commissioners and/or providers. Commissioners and providers are reminded that it is their responsibility to implement the guidance, in their local context, in light of their duties to have due regard to the need to eliminate unlawful discrimination, advance equality of opportunity, and foster good relations. Nothing in this guidance should be interpreted in a way that would be inconsistent with compliance with those duties.

Implementation of the Guideline

Description of Implementation Strategy

The National Institute for Health and Care Excellence (NICE) will support this guidance through a range of activities to promote the recommendations for further research. The research proposed will be considered by the NICE Medical Technologies Evaluation Programme research facilitation team for the development of specific research study protocols as appropriate. NICE will also incorporate the research recommendations into its guidance research recommendations database (available on the NICE Web site) and highlight these recommendations to public research bodies.

Implementation Tools

Foreign Language Translations

Mobile Device Resources

Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

National Institute for Health and Care Excellence (NICE). Therapeutic monitoring of TNF-alpha inhibitors in Crohn's disease (LISA-TRACKER ELISA kits, IDKmonitor ELISA kits, and Promonitor ELISA kits). London (UK): National Institute for Health and Care Excellence (NICE); 2016 Feb 17. 52 p. (Diagnostics guidance; no. 22).

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Feb 17

Guideline Developer(s)

National Institute for Health and Care Excellence (NICE) - National Government Agency [Non-U.S.]

Source(s) of Funding

National Institute for Health and Care Excellence (NICE)

Guideline Committee

Diagnostics Advisory Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Committee members are required to submit a declaration of interests on appointment, in every year of their tenure, and at each Committee meeting, in line with the National Institute for Health and Care Excellence's (NICE's) code of practice for declaring and dealing with conflicts of interest.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the National Institute for Health and Care Excellence (NICE) Web site . Also available for download in ePub or eBook formats from the NICE Web site .

Availability of Companion Documents

The following are available:

- Diagnostics Assessment Programme. Crohn's disease: tests for therapeutic monitoring of TNF inhibitors (LISATRACKER ELISA kits, TNFα-Blocker ELISA kits, and Promonitor ELISA kits). Diagnostics assessment report. London (UK): National Institute for Health and Care Excellence (NICE); 2015 May. 485 p. Available from the NICE Web site .

- Diagnostics Assessment Programme manual. London (UK): National Institute for Health and Care Excellence; 2011 Dec. 130 p. Available from the NICE Web site.

Patient Resources

The following is available:

- Therapeutic monitoring of TNF-alpha inhibitors in Crohn's disease (LISA-TRACKER ELISA kits, IDKmonitor ELISA kits, and Promonitor ELISA kits). Information for the public. London (UK): National Institute for Health and Care Excellence (NICE); 2016 Feb. (Diagnostics guidance; no. 22). Available from the National Institute for Health and Care Excellence (NICE) Web site. Also available in Welsh from the NICE Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

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